holin opens the pores in the cytoplasmic membrane, allowing endolysin to reach and cleave specific peptidoglycan bonds, causing the disruption of the cell wall structure. As a consequence, the internal osmotic pressure is affected and the cell is disrupted by through hypotonic lysis through a process called "lysis from within" (Figure 15.1i). In tailed phages, the endolysin-mediated lysis is generally preceded by the holin action. This means that while endolysins accumulate in the cytosol, holins oligomerize to permeabilize the cytoplasm, exposing the peptidoglycan to the endolysins (Wang et al. 2000).

After the action of these two enzymes (spanins may also be required), the mature phage progeny particles are able to find new hosts to start new infection cycles (Figure 15.1a). All these proteins involved in the phage lytic cycle have their specific and indispensable role in the process of bacteria predation improved through millions of years of evolution, and their function can thus be used to combat the antibiotic resistance crisis. We will describe in the next sections the proteins that present the higher antimicrobial potential (Figure 15.2).

## 15.2 Polysaccharide Depolymerases

To initiate infection, phages need to recognize specific ligands on the host bacterial cell surface through receptor binding proteins (Figure 15.1a); in some cases, phage recognition involves enzymatic degradation of extracellular bacterial polysaccharides present in the K (capsule) and O (outermost portion of the lipopolysaccharides [LPS], usually present in Gram-negative bacteria) antigens (Bertozzi Silva et al. 2016). While some bacteria have evolved to produce a surrounding capsule that mask and hide these receptors, phages co-evolved to encode enzymes that specifically recognize and degrade those capsules (using it as their primary receptor) exposing the second receptor and allowing an irreversible binding and consequent infection (Bertozzi Silva et al. 2016). These enzymatic functions are accomplished by the phage-encoded depolymerases (Figure 15.2), which recognize and degrade the bacterial surface polysaccharides (K- and O-antigens) as well as exopolysaccharides (EPS).

In our current knowledge, only a few phages encode polysaccharide depolymerases. The presence of these enzymes was first described in 1956 after the observation of growing haloes surrounding the phage plaques during the spot-on-lawn method (Adams and Park 1956).

Depolymerases are integrated at the virion particle, usually associated with the phage tail spikes (Figure 15.2). Therefore, these molecules have high genetic plasticity allowing degradation of a vast variability of polymorphic O- and K-antigens of their hosts. For instance, *Escherichia coli* has 186 O and 80 K forms defined by serology (Whitfield and Roberts 1999), which means that in nature, phages infecting *E. coli* should encode depolymerases to recognize and degrade all these antigens.